OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE

By

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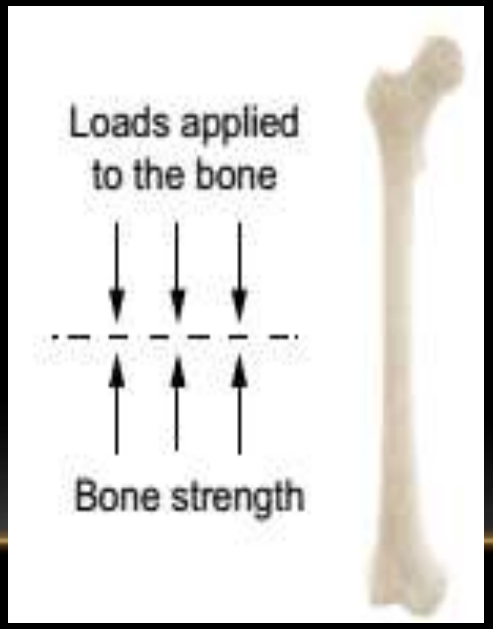
OSTEOPOROSIS (POROUS BONE)

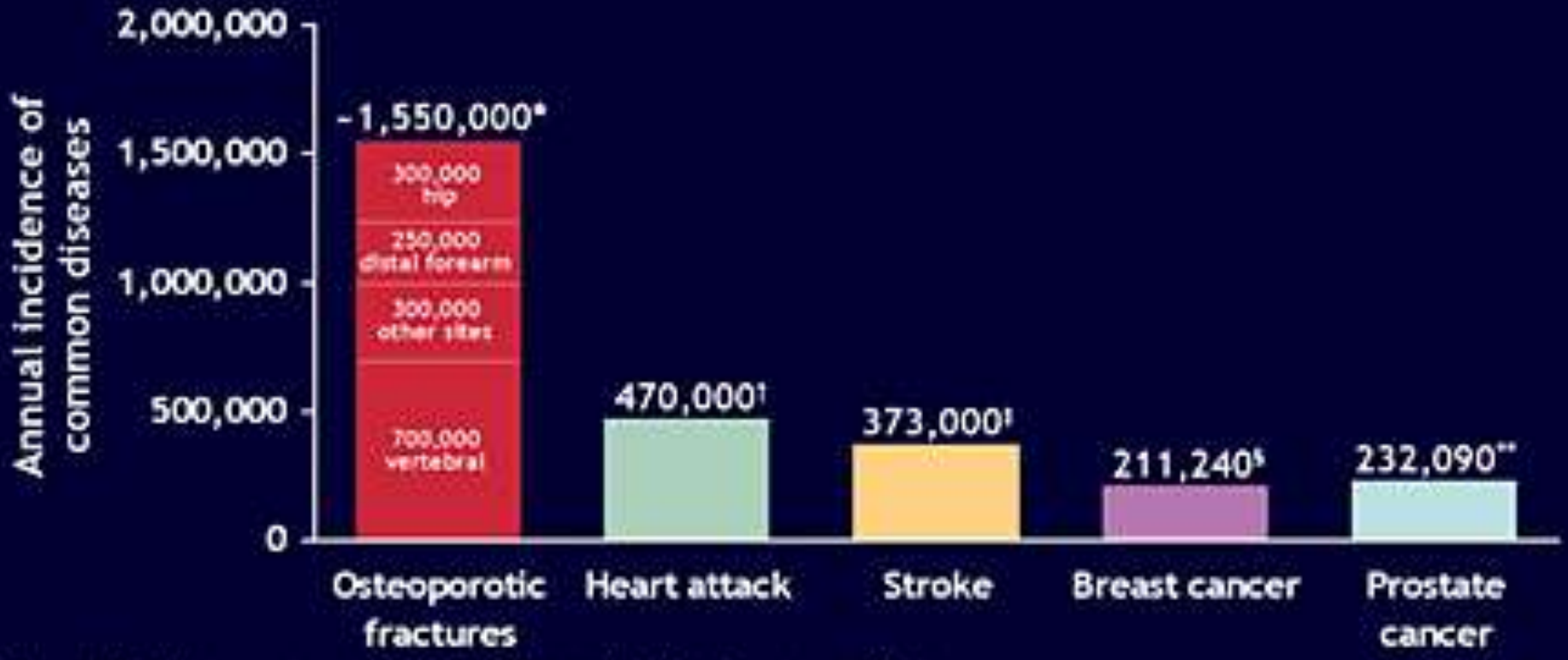
Progressive systemic skeletal disease :

- Low bone mass (mineral & matrix)
- Microarchitectural deterioration
- Increase in bone fragility
- Susceptibility to fracture



Kanis JA et al .,1994. J Bone Miner Res 9:1137-1141

Osteoporosis Fracture Incidence vs Incidence of Heart Attack, Stroke, Breast Cancer, and Prostate Cancer



*Annual incidence women all ages; †Annual estimate women 29+;
‡Annual estimate women 30+; §2005 new cases: women of all ages; **2005 new cases: men of all ages

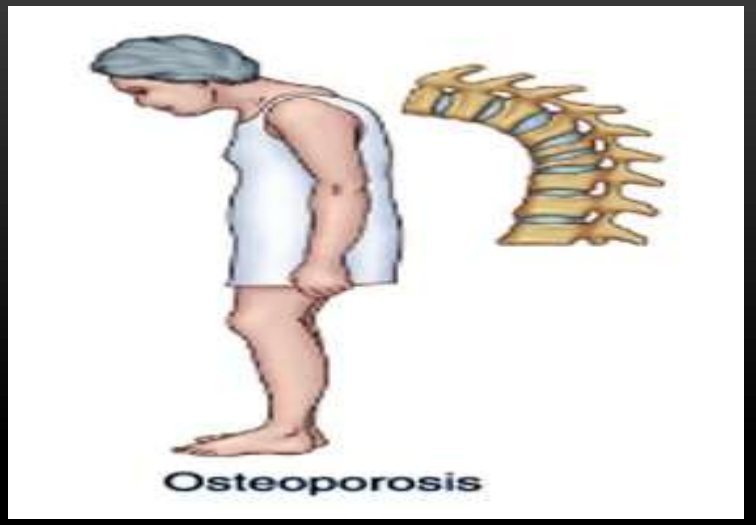
National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. Washington, DC: National Osteoporosis Foundation. 2003.
American Heart Association. *Heart & Stroke Facts*. Dallas, TX: American Heart Association 2003.
American Cancer Society. *Cancer Facts & Figures 2005*. Atlanta, GA: American Cancer Society 2005.

Osteoporosis was previously thought to be a part of the normal aging process

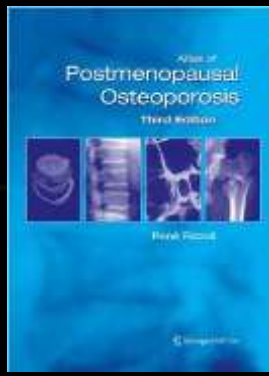
OSTEOPOROSIS - "A SILENT KILLER". A REVIEW OF THE CURRENT LITERATURE FROM CLINICIAN AND PHYSIOTHERAPIST PERSPECTIVE

JANUSZ KOCJAN

Medical University of Silesia, Faculty of Medicine, Katowice, Poland



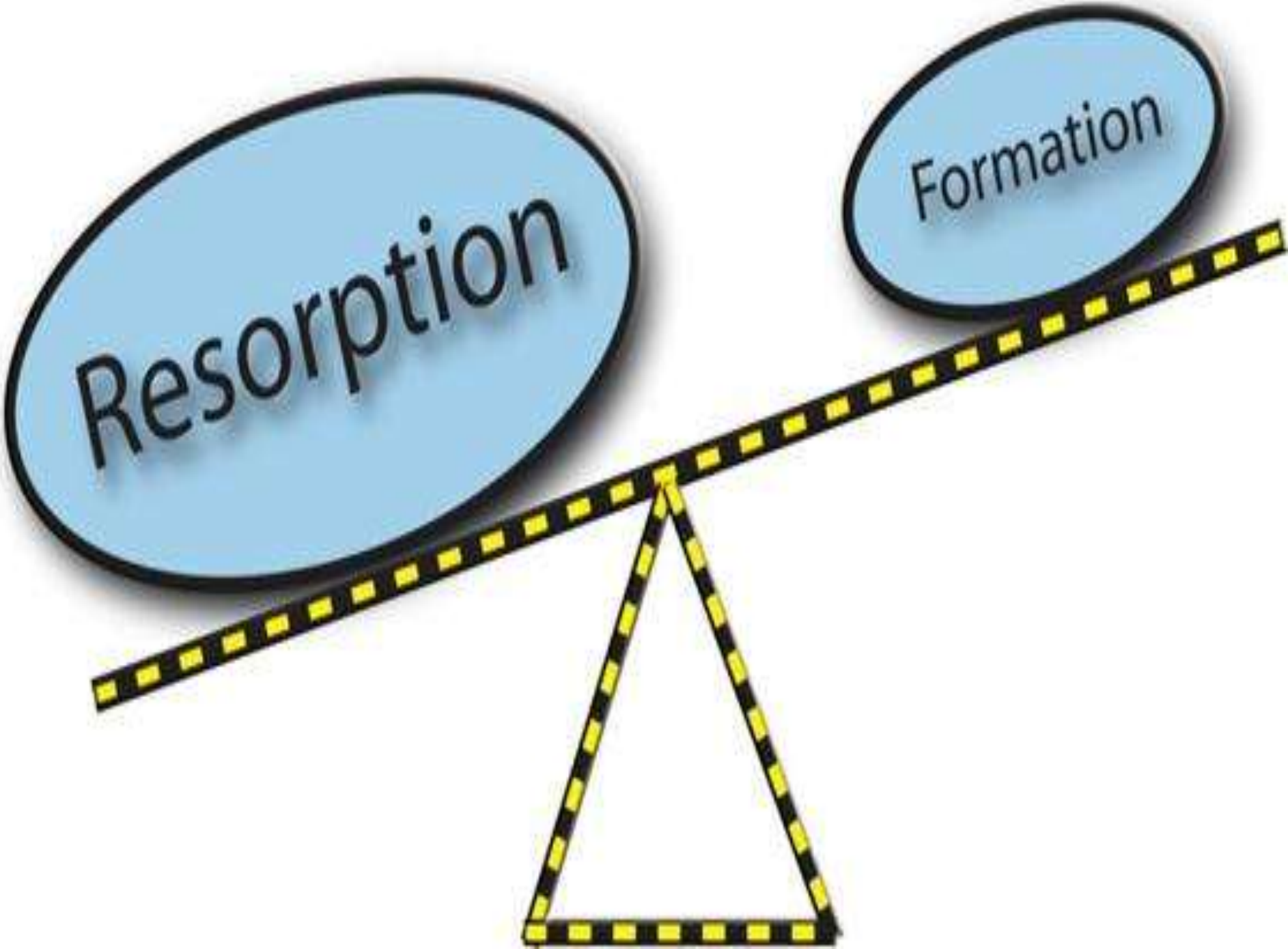
Loss of height, pain



50% of patients with hip fracture can no longer live independently
20% die within 12 months of the fracture
↑ in CKD patients

Aging is Associated with:

- Reductions in GFR
- Increased prevalence of osteoporosis


Resorption
Formation

WHO Fracture Risk Assessment Tool **FRAX®**

10-year probability of fracture in untreated patients

www.shef.ac.uk/FRAX

- Age
- Gender
- Weight
- Height
- Clinical risk factors
  - Previous fragility fracture
  - Parental history of hip fracture
  - Current smoking
  - Glucocorticoid treatment
  - Rheumatoid arthritis
  - [Other secondary causes of osteoporosis]
  - Alcohol intake 3 or more per day
- Femoral Neck BMD [or Body Mass Index]

ORIGINAL INVESTIGATION

Renal Function and Risk of Hip and Vertebral Fractures in Older Women

Kristine E. Ensrud, MD, MPH; Li-Ying Lui, MA, MS; Brent C. Taylor, PhD; Areef Ishani, MD, MS; Michael G. Shlipak, MD, MPH; Katie L. Stone, PhD; Jane A. Cauley, DrPH; Sophie A. Jamal, MD, PhD; Diana M. Antoniucci, MD; Steven R. Cummings, MD; for the Study of Osteoporotic Fractures Research Group

2007

- Reduced renal function in older women is associated with higher rates of hip fracture
- The risk of hip fracture in stage 5 is four times higher than in age matched controls

Common metabolic bone diseases associated with fragility fractures

Osteoporosis
(including all secondary causes of osteoporosis, including steroid-induced osteoporosis, after solid organ transplantation)

Osteogenesis imperfecta

Osteomalacia

Osteitis fibrosa cystica (severe)
Pathologic fractures (malignancies)

Severe renal failure (renal osteodystrophy)
- Osteoporosis
- Osteitis fibrosa cystica
- Osteomalacia
- Mixed osteodystrophy
- Adynamic bone disease, including aluminum bone disease
- Amyloid bone disease

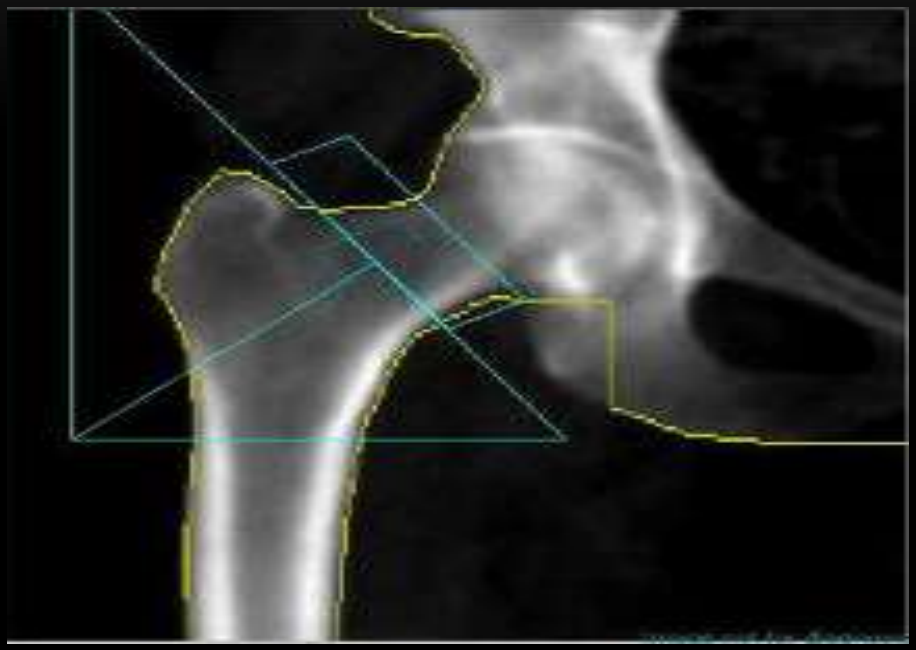
Osteopetrosis

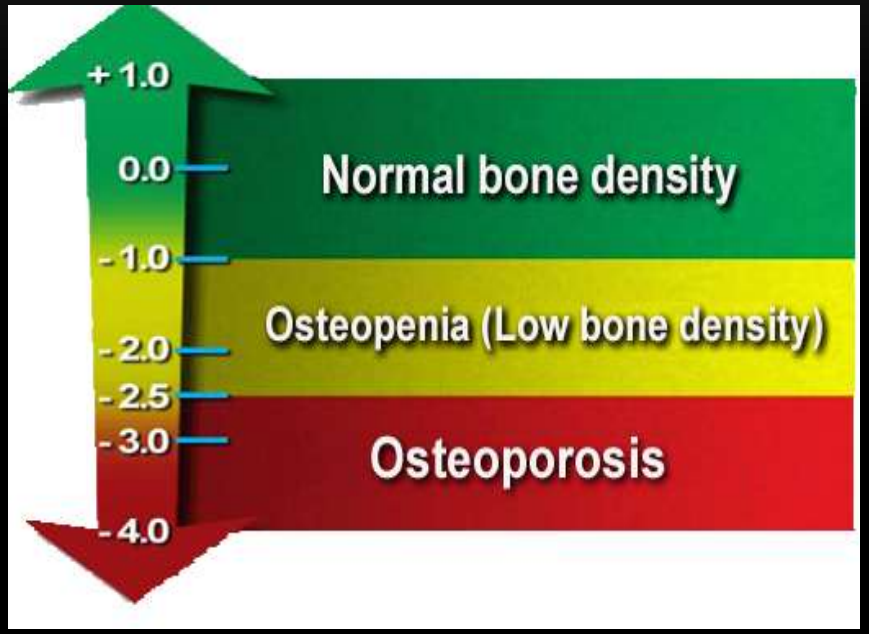
Paget disease of bone

OSTEOPOROSIS

- Low-trauma fractures
- T scores

T-SCORE





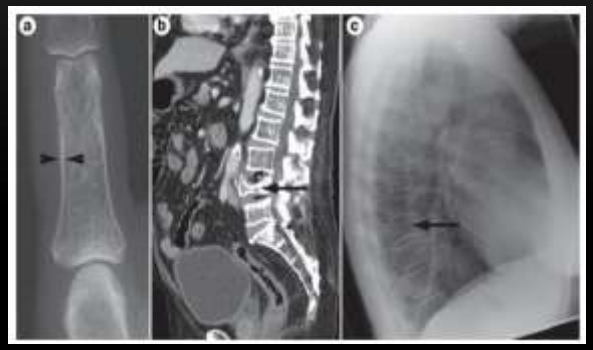
Use of BMD at the proximal femur is favourable

A low T score :

Osteoporosis/ non osteoporotic bone diseases

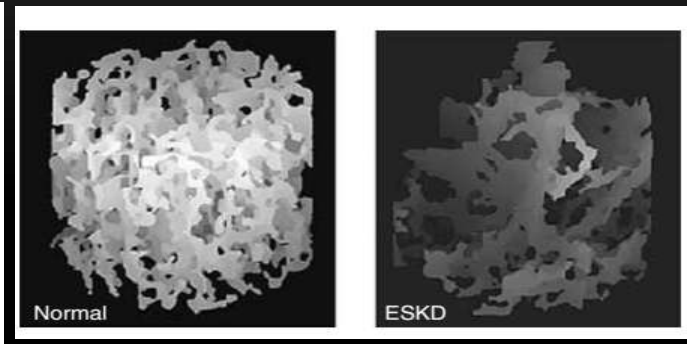
Problematic in CKD patients (stage 4-5)

Non-invasive bone imaging technologies in CKD patients

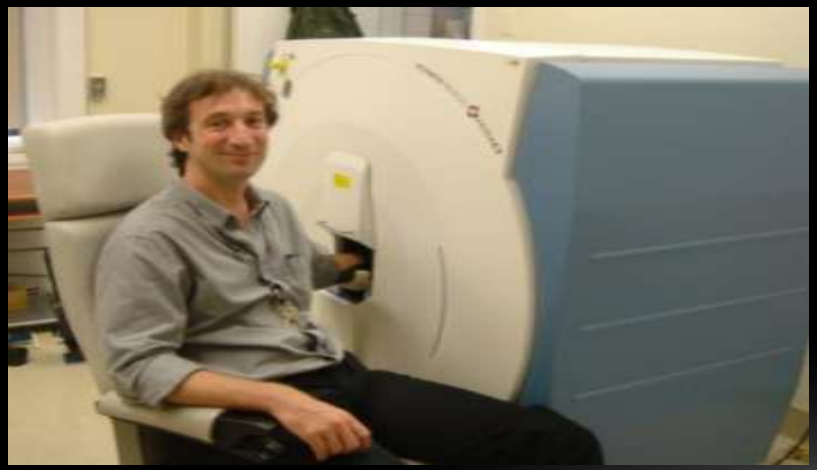


CT

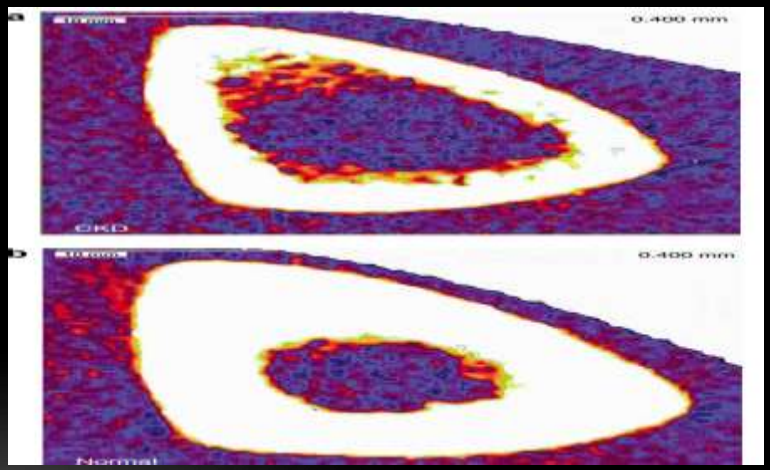
Quantitative ultrasound



Micro-MRI



High Resolution Peripheral QCT



Peripheral QCT

Adams, J. E. *Nat. Rev. Endocrinol.* 9, 28–42 (2013)

Non-invasive bone imaging technologies in CKD patients

- Bone microarchitecture
- New way to classify skeletal strength
- Not discriminating between osteoporosis and renal osteodystrophy

Adams, J. E. *Nat. Rev. Endocrinol.* 9, 28–42 (2013)

BONE TURNOVER MARKERS

- Tartrate-resistant acid phosphatase 5b (TRAP 5b), a marker of osteoclast activity, holds promise for assessing the activity of this bone remodeling cell in patients with chronic kidney disease–mineral and bone disorder
- Sclerostin

Hartmut H et al, Clin J Am Soc Nephrol 9: 2014

BONE BIOPSY

If bone turnover markers suggest low bone turnover, bone biopsy is necessary before starting an antiresorptive agent

- Stages 1 through 3 CKD: the absence of aberrant biochemical tests suggesting CKD-MBD
- The distinction between osteoporosis and CKD-MBD becomes more difficult in stages 4 and 5 through 5D CKD
- In fracturing patients ,severe CKD:

  careful assessment of bone turnover markers

  bone biopsy

Paul,Seminars in Nephrology, 2009.29 (2):144–155

Treatment

PREVENTING FALLS

Visual acuity

Medication that alters alertness and balance

Handrails

HOME ENVIRONMENTAL HAZARDS

Slippery floors

Obstacles

Insufficient lighting

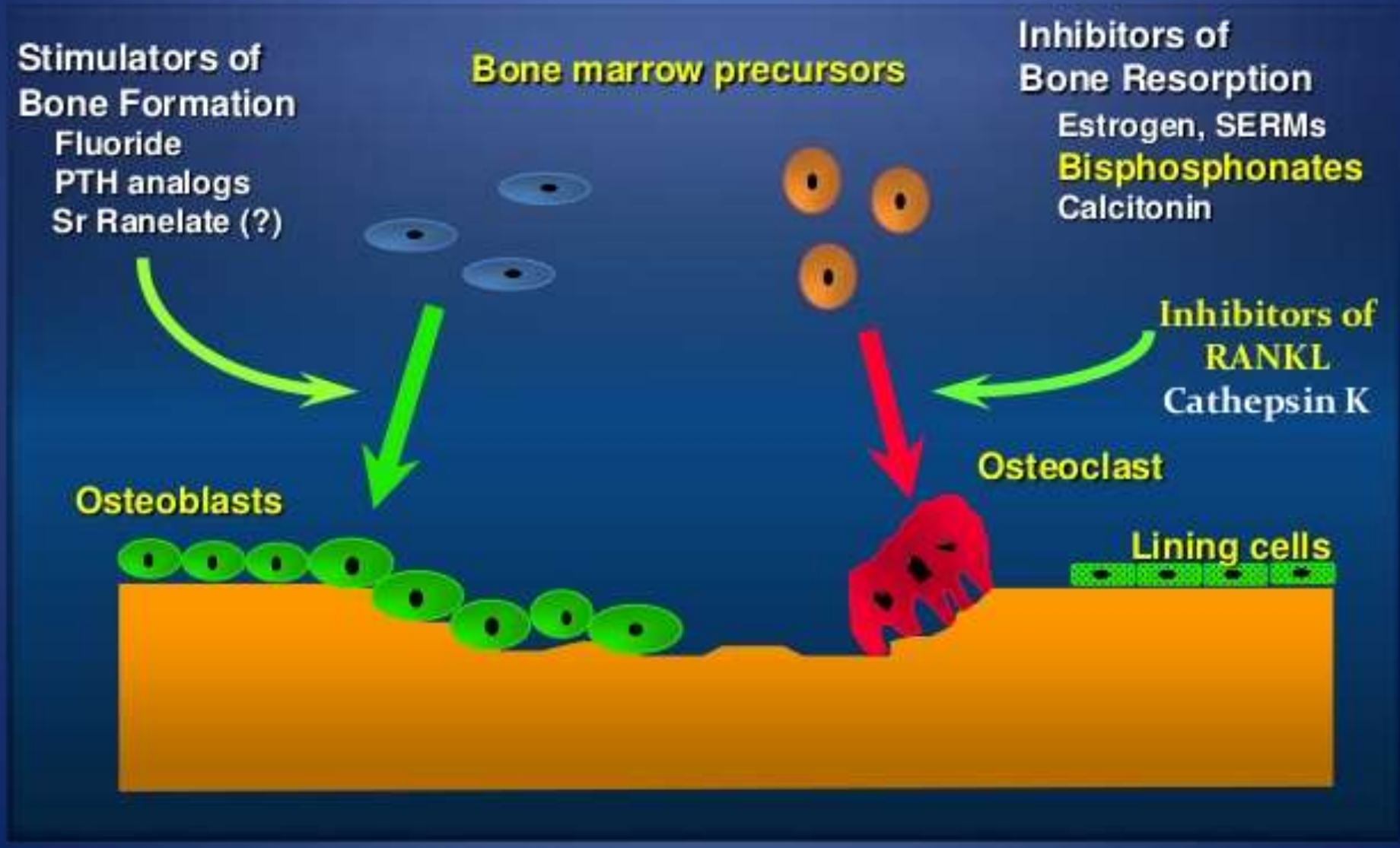
- Calcium and vitamin D supplementation

  Optimal calcium intake of 1200mg daily

  Optimal 25 (OH) D levels
- Protein intake
- Regular weight-bearing exercise

HIP PROTECTORS

Therapeutic strategies



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 4, 2007
Published online on January 22, 2007; doi: 10.1359/JBMR.070112

Alendronate Treatment in Women With Normal to Severely Impaired Renal Function: An Analysis of the Fracture Intervention Trial*

Sophie A Jamal,[1] Douglas C Bauer,[2] Kristine E Ensrud,[3] Jane A Cauley,[4] Marc Hochberg,[5] Areef Ishani,[3] and Steven R Cummings[2]

- Women participating in the Fracture Intervention Trial (*n* =6458)
- A randomized controlled trial of alendronate / placebo

Conclusion: Alendronate can be prescribed to older women with reduced e GFR, but not end-stage renal failure

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 12, 2005
Published online on August 22, 2005; doi: 10.1359/JBMR.050817

Safety and Efficacy of Risedronate in Patients With Age-Related Reduced Renal Function as Estimated by the Cockcroft and Gault Method: A Pooled Analysis of Nine Clinical Trials

Paul D Miller,[1] Christian Roux,[2] Steven Boonen,[3] Ian P Barton,[4] Lisa E Dunlap,[4] and David E Burgio[4]

- Risedronate 5 mg daily was safe and effective even in women with severe renal impairment (CrCl < 30 ml/min).
- Additional studies are needed to establish the safety and efficacy of risedronate treatment in patients ESRD or stage 5 CKD (GFR < 15 ml/min)

BISPHOSPHONATES

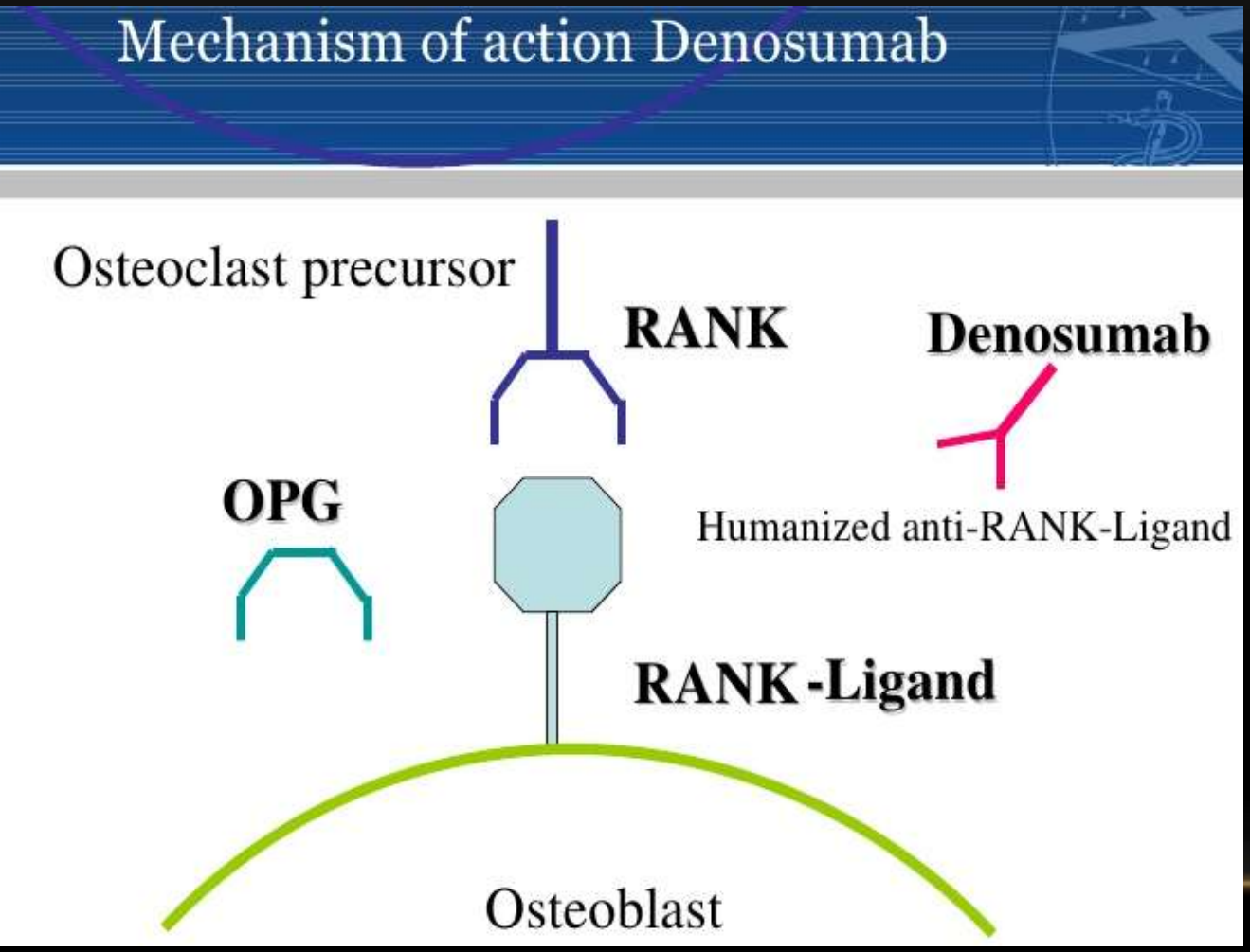
No data on patients with stage 5 CKD (GFR <15 mL/min)

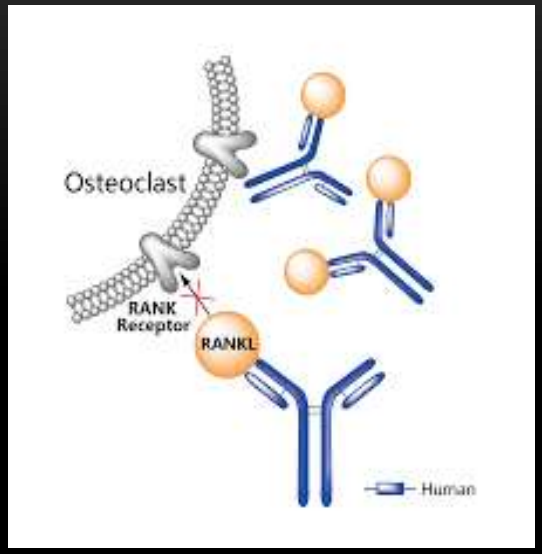
Use only in very specific circumstances

- Fragility fractures
- Half of standard dose for PMO, for no longer than 2-3 years

Miller PD Semin Dial 2007

DENOSUMAB


Mechanism of action Denosumab
Osteoclast precursor
RANK
Denosumab
OPG
Humanized anti-RANK-Ligand
RANK-Ligand
Osteoblast


Osteoclast
RANK
Receptor
RANKL
Human


XGEVA
(denosumab)
120
℞ Only

Effects of Denosumab on Fracture and Bone Mineral Density by Level of Kidney Function

Sophie A Jamal,[1] Östen Ljunggren,[2] Catherine Stehman-Breen,[3] Steven Ron Cummings,[4] Michael R McClung,[5] Stefan Goemaere,[6] Peter R Ebeling,[7] Edward Franek,[8] Yu-ching Yang,[3] Ogo I Egbuna,[3] Steven Boonen,[9] and Paul D Miller[10]

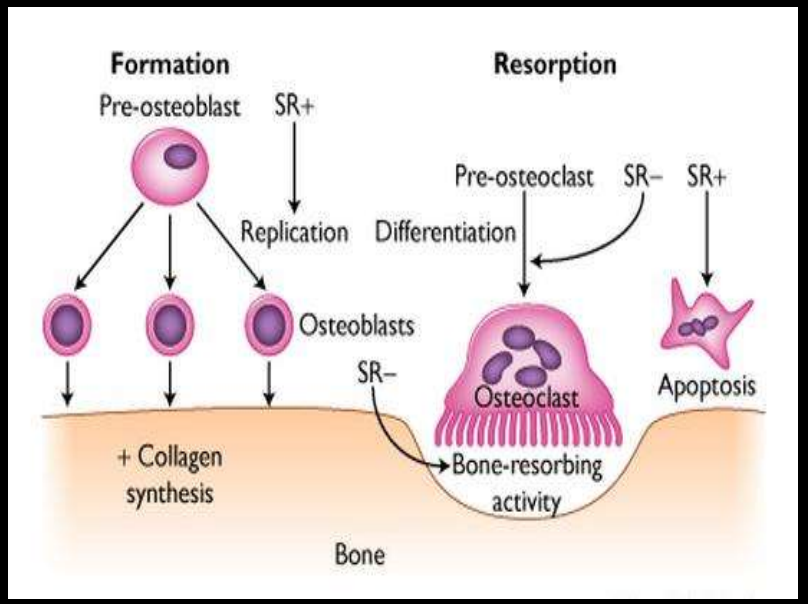
(2011)

- FREEDOM Trial
- 3902 received denosumab (DMAb), and 3906 received placebo.

Conclusion :DMAb is safe and likely effective at reducing fracture risk and increasing BMD in women with postmenopausal osteoporosis and stage 1 to 3 CKD. Although the sample size of subjects with stage 4 CKD was small, our analysis suggests that the benefits are directionally similar

STRONTIUM RANELATE

- Both anti-resorptive and mild anabolic.
- Postmenopausal osteoporosis
- Not recommended for late CKD.



RALOXIFENE

CLINICAL RESEARCH www.jasn.org

The Effect of Raloxifene Treatment in Postmenopausal Women with CKD

2008

Areef Ishani,* Terri Blackwell,† Sophie A. Jamal,‡ Steven R. Cummings,† and Kristine E. Ensrud,* for the MORE Investigators

Raloxifene increases BMD at both the hip and the spine and reduces the risk for vertebral fractures among individuals with mild to moderate CKD

CALCITONIN

- Prescribed regardless of CKD stage fracture
- For patients for whom alternative treatments are not suitable
- ↑Malignancy risk

TERIPARATIDE

Osteoporos Int. 2007 Jan;18(1):59-68. Epub 2006 Sep 30.

Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment.

Miller PD[1], Schwartz EN, Chen P, Misurski DA, Krege JH.

- No adverse effect on GFR in patients with mild to moderate renal impairment
- GFR goes up a little because PTH is a vasodialator and increases renal blood flow.
- There is no data on use of PTH in patients with GFR <30 mL/min

Management in Stage 5 CKD in Fracturing Patients

- No Data
- Only Opinion

2016 Medicines in Development for Osteoporosis

Drug Name	Sponsor	Indication	Development Phase
abaloparatide (synthetic peptide analog of human parathyroid hormone-related protein)	Radius Health *Waltham, MA*	postmenopausal osteoporosis (subcutaneous injection)	Phase III www.radiuspharm.com
		postmenopausal osteoporosis (transdermal patch)	Phase II completed www.radiuspharm.com
blosozumab (SOST protein inhibitor)	Eli Lilly *Indianapolis, IN*	postmenopausal osteoporosis	Phase I www.lilly.com
DS-1501 (anti-siglec-15 antibody)	Daiichi Sankyo *Parsippany, NJ*	osteoporosis	Phase I www.dsi.com
odanacatib (cathepsin K inhibitor)	Merck *Kenilworth, NJ*	male osteoporosis, postmenopausal osteoporosis	Phase III www.merck.com
		corticosteroid-induced osteoporosis	Phase I www.merck.com
Prolia® denosumab	Amgen *Thousand Oaks, CA*	corticosteroid-induced osteoporosis	Phase III www.amgen.com
romosozumab (SOST protein inhibitor)	Amgen *Thousand Oaks, CA* UCB *Smyrna, GA*	male osteoporosis, postmenopausal osteoporosis	Phase III www.amgen.com www.ucb-usa.com

Need for New
OSTEOPOROSIS TREATMENTS

The development of new treatments for osteoporosis will become even more important as prevalence of the disease and low bone mass in people over the age of 50 is expected to increase in the next 15 years. In 2015, an estimated 54 million American adults had osteoporosis or low bone mass, but that number could grow to 64 million in 2020 and 71 million in 2030.

EXPECTED GROWTH IN OSTEOPOROSIS PREVALENCE

Source: National Osteoporosis Foundation, Journal of Bone and Mineral Research, The Recent Prevalence of Osteoporosis and Low Bone Mass in the United States Based on Bone Mineral Density at the Femoral Neck or Lumbar Spine," 2014.

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